VIRGINIA INHALATION TOXICOLOGY ADVISORY GROUP

MINUTES-UNAPPROVED DRAFT

SIXTH MEETING
September 9, 2009

TIME AND PLACE: 10:00AM – 1:00 PM
DEQ Central Office
629 E. Main Street
Richmond, VA 22469
2nd Floor Conference Room

PRESIDING: Patricia McMurray, DEQ Risk Assessor Program Manager

MEMBERS PRESENT:

Jim Gould, Sierra Club
Chris Bednar, Smurfit Stone
John Morris, Ph.D., University of Connecticut (SOT)
Debbie Mulrooney, DuPont (VMA) – by phone
Kevin Wallace, M. D., University of Virginia – by phone
Kimber White, Ph. D., Virginia Commonwealth University
Robert Corley, Ph.D., Virginia State University
Dwight Flammia, Ph.D., Virginia Department of Health

DEQ STAFF PRESENT:

Patty Buonviri, Air Toxics Coordinator (Recorder)
Sonal Iyer, Risk Assessor, Office of Waste Technical Support

GUESTS PRESENT: None

Net Connect was used to link those participating by telephone.

A motion was made and seconded to approve the minutes from the July 30, 2009 meeting as written. DEQ staff will post the minutes on the Virginia Town Hall within three days of approval. See http://www.townhall.state.va.us/L/meetings.cfm for the minutes from previous meetings.

ACTION DEQ: Obtain studies on ethylene dibromide and n-hexane and distribute to VINTAG members for review.

DEQ obtained and distributed study information on September 1, 2009 for two chemicals (Ethylene Dibromide and n-Hexane) because a more in depth review was necessary. A

copy of a summary sheet for each pollutant was also provided by DEQ via email prior to the meeting. A copy of the summary sheet for each pollutant is attached.

Ethylene Dibromide

One member noted that there was a 10 fold difference between the EPA (9 ug/m^3) and Cal EPA (0.8 ug/m^3) number. One member expressed concern with the human study used by CAL EPA because there was some dermal exposure that couldn't be quantified and that perhaps the dermal exposure may have contributed to the sperm abnormalities. The study indicated that no respirators or other protective gear was worn by the workers. However, another member thought that there would be little opportunity for direct skin exposure. Although there must have been some dermal exposure as the field workers did exhibit moderate skin effects.

One member observed that the animal study (non dermal) used by EPA showed testicular degeneration. However, the study didn't look at sperm count. One member thought that there would need to be a compelling reason to use a less conservative number. The members agreed they could accept the hypothesis of human study but note the limitations of the data. One member thought the human study is supported by the animal study. After much discussion, the group opted to take the risk conservative approach by recommending the Cal EPA value of 0.8 ug/m^3. The group thought it was reasonable to accept the lower limit but not necessarily the study.

n-Hexane

One member questioned whether the proteins that were reduced in the rat study used by EPA are relevant for humans. Another member noted that the decrease in proteins wasn't used as a critical effect to determine their value. Another member questioned the human study used by Cal EPA because of the co exposure with other forms of hexane and with acetone. However, one member noted that Cal EPA did not use the human studies quantitatively to develop their number.

One member pointed out that both studies showed the same dose response relationships and that the difference in the values was based on the uncertainty factors that were applied.

Because of the differences in values for Cal EPA (7000 ug/m^3) and EPA (700 ug/m^3), the group decided to look at the ASTDR value. It was noted that ASTDR uses a value of 2000 ug/m^3which is in between the Cal EPA and EPA values.

One member commented on the duration of the animal study that Cal EPA used. The rats were exposed 6 days per week for one year. The member noted that a year long study is longer than normal and would be inclined to go with the higher (less protective) value.

One member observed that EPA used a less than lifetime uncertainty factor, but that the longer study used by Cal EPA resulted in a higher number. The member thought that the uncertainty factor used by EPA may not be necessary.

One member stated that practically speaking most industries use a hexane mixture rather than pure n-hexane because it is less expensive.

DEQ told the group that EPA typically adds a database uncertainty factor when developmental neurotoxicity and multigenerational reproductive studies are lacking. Under the most recent guidance Cal EPA will be adding these UFs also.

One member noted that it is the additional UF that makes EPA's number lower and that if the studies had the same LOAEL and NOAEL then there would be less concern about the difference in the uncertainty factors. One member stated that the animal studies are all consistent in that exposure between 200 to 500 ppm will show effects.

One member thought if we accept that the human LOAEL is 58 ppm, the value would be closer to the ASTDR value of 2118 ug/m^3 (0.6 ppm) and in this case it seems reasonable to use the intermediate number. One member wondered what the current DEQ SAAC values were. The hourly SAAC is 8800 ug/$m^3$and the annual value is 352 ug/m^3.

Another member commented that EPA's review (2005 vs 2001 for Cal EPA) is the more recent of the two. One member thought it would be hard to justify Cal EPA's value of 7000 ug/m3 when the current DEQ SAAC is 352 ug/m^3.

After considerable discussion, an extensive review, and considering pros and cons of each study, the group reached consensus to recommend EPA's value of 700 ug/m^3. One member noted that New Jersey and Michigan are also using 700 ug/m^3.

15 minute break

Review of draft VINTAG report and spreadsheets

DEQ provided members with a copy of a draft report titled "The Virginia Inhalation Toxicology Advisory Group (VINTAG) Process and Recommendations" and referenced spreadsheets. DEQ reviewed the report with the members and members provided suggestions for revisions.

NEW ACTION DEQ: DEQ will make revisions and send out to the group for a final review. One member requested that DEQ highlight the changes that were made before sending to VINTAG members.

Each VINTAG member will send DEQ an email to acknowledge approval of the final report.

DEQ noted that the next steps will be made by DEQ and include calculating new SAAC numbers and presenting to management. These steps are all independent of VINTAG.

DEQ thanked the members for all of their time, effort, input, presentations, and the use of Net Connect.

VINTAG members commended DEQ for good time management of the project and noted that they learned a lot from this experience.

DEQ anticipates having a final report to share with DEQ management by late October or early November 2009.

Meeting adjourned at 1:00 PM

ETHYLENE DIBROMIDE (106-93-4)
[1,2-dibromomethane]

California (2001):

Chronic REL 0.8 ug/m^3

Derivative Information:

- Study—Ratcliff, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., and Hornung, R. W. 1987. Semen quality in papaya workers with long term exposure to ethylene dibromide. Br. J. Ind. Med. 44:317-326.
- Study Format—variable workplace breathing zone airborne exposure (88 ppb geometric average [TWA] exposure with peak exposure up to 262 ppb). Average exposure duration 4.9 years, standard deviation 3.6 years.
- Critical Effects—reproductive toxicity; decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) in human males.
- LOAEL—88 ppb (676 ug/m^3)
- NOAEL—not observed
- $LOAEL_{HEC}$—31 ppb (238 ug/m^3)
- Uncertainty factors:
    1. LOAEL uncertainty factor 10
    2. subchronic uncertainty factor 3
    3. interspecies uncertainty factor 1
    4. intraspecies uncertainty factor 10
    5. cumulative uncertainty factor 300

US EPA (2004)

RFC 9 ug/m^3

Derivation Information:

- Study—NTP (National Toxicology Program). 1982. Carcinogenesis bioassay of 1,2-dibromomethane (CAS No. 106-93-4) in F344 rats and B6C3F1 mice (inhalation study). NTIS no. PB82-181710.
- Study format—male and female Fischer 344 rats and B6CF3 mice (n=50 per sex, species, and exposure group) were exposed to 0, 10 or 40 ppm (0, 77 or 307 mg/m3) 1, 2-dibromomethane for 6 hr/day, 5 days/week. The study was designed to assess potential adverse effects of 1,2-dibromomethane following 103 weeks of exposure.

- Critical effects—noncarcinogenic effects were hepatic necrosis (male and female rats), testicular degeneration (male rats), retinal atrophy (female rats), adrenal cortical degeneration (female rats), splenic hematopoiesis (female mice), and inflammation of the nasal cavity (female mice). [Note: High exposure rats of both sexes and female mice exhibited high mortality (80-90 percent) beginning at about 60 weeks, resulting in early termination (between 78 and 91 weeks) of these exposure groups. The low exposure groups were not terminated until the end of the study (104-106 weeks) though the low exposure female mice displayed high mortality (62 per cent) relative to controls (20 per cent mortality). The male mouse study was not considered relevant for derivation of an RFC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure-related.]
- LOAEL—76.8 mg/m^3 (nasal inflammation)
- NOAEL—not observed
- $BMDL_{10\ HEC}$—2.8 mg/m^3 (nasal inflammation)
- Uncertainty factors:
    1. interhuman uncertainty 10
    2. animal to human uncertainty 3
    3. incomplete data uncertainty 10
    4. cumulative uncertainty 300

Discussion:

From the California document "Chronic Toxicity Summary—Ethylene Dibromide" page A-42:

"The strengths of the inhalation REL for ethylene dibromide include the use of human exposure data from workers exposed over a period of years, and the presence of the toxic endpoint (male reproductive system) in several experimental animal species. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating occupational exposure, the potential variability in occupational exposure concentration, and the limited nature of the study (fertility was not actually tested). The database for chronic toxicity of EDB in experimental animals would be enhanced if the proper doses were chosen to determine a NOAEL."

From the US EPA document "Toxicological Review of 1, 2-dibromomethane" page 14:

"Ratcliffe, et al. (1987) reported summary air exposure data, but there was moderate dermal exposure that could not be quantified (Schrader et al., 1988). Semen of exposed workers exhibited significantly decreased average sperm count per ejaculate and percentage of viable and motile sperm. There were statistical increases in certain types of morphological abnormalities (tapered heads, absent heads, and abnormal tails) in exposed workers. There was also a significant increase in percentage of subjects with sperm counts fewer than 20 million in exposed workers (21.7 per cent compared to 4.7

per cent in controls). The highly variable inhalation exposures and the confounding dermal exposures preclude the use of this population for the development of an RFC."

U. S. EPA did not use the human study due to concerns about dermal exposure and highly variable inhalation exposure. The VINTAG requested to see the critical studies to get more information about the dermal exposure. The Ratcliffe study does not give any detail about the dermal exposure except to say "No respirators or other personal protective equipment are used. There is little opportunity for skin exposure except for accidental spillages of liquid EDB." (See page 318, Description of Plants). According to EPA's Toxicological Summary "Schrader et al. (1988) stated that dermal exposure in forestry workers was excessive, and the papaya workers described in Ratcliffe et al. (1987) were subject to moderate dermal exposure." (Note that Schrader was one of the authors on the Ratcliffe study.)

Also note that the NTP study used by U. S. EPA also showed effects in the male reproductive system (testicular degeneration in rats). However, the BMDL for nasal inflammation was lower than the BMDL that EPA calculated for testicular degeneration so it was not used for setting the RfD. The NTP study did not look at sperm count.

ATSDR (1992) did not calculate an MRL for ethylene dibromide due to lack of quantitative exposure data. On reproductive effects ATSDR notes the following: "Two types of human studies have been reported in the literature: one that assessed fertility differences between groups of workers (Wong et al. 1979)and others that assessed the potential antispermatogenic effects in male workers (Ratcliffe et al. 1987; Ter Haar 1980). These studies provided little or equivocal evidence that 1, 2-dibromoethane exposure was associated with adverse fertility or antispermatogenic effects in exposed workers. All studies lacked sufficient statistical power to detect an association due to small sample size, inadequate exposure assessment or histories, inappropriate control groups, and a general methodological weakness in assessing fertility status and antispermatogenic effects. Nevertheless, they do provide some indication of potential adverse effects of 1, 2-dibromoethane on fertility and sperm production."

California (2001):

Chronic REL 7000 ug/m^3

Derivative Information:

- Studies—one experimental study and two occupational studies:
  1. experimental—Miyagaki, H. 1967. Electrophysiological studies on the peripheral neurotoxicity of n-hexane. Jap. J. Ind. Health 9(12-23): 660-671.
  2. occupational:
     - Chang, C. M., Yu, C. W., Fong, K. Y., Leung, S. Y., Tsin, T. W., Yu, Y. L., Cheung, T. F., and Chan, S. Y. 1993. N-hexane neuropathy in offset printers. J. Neurol. Neurosurg. Psychiatry. 56(5):538-542.
     - Sanagi, S., Seki, Y., Sugimoto, K. et al. 1980. Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int. Arch. Occup. Environ. Health. 47:69:79.
- Study Formats:
  1. experimental—Miyagaki—male SM-A strain mice (10 per group) were exposed continuously to 0, 100, 250, 500, 1000 or 2000 ppm commercial grade hexane (65 to 70 per cent n-hexane with the remainder being other hexane isomers) for 6 days/week for one year.
  2. occupational:
     - Chang—workers exposed to 80 to 210 ppm hexane (mean of 132 ppm), 20 to 680 ppm isopropanol (mean of 235 ppm), and 20 to 84 ppm (mean of 50 ppm) toluene. The workers worked 12 hours per day for six days per week. The mean duration of employment was 2.6 years, with a range of one month to 30 years.
     - Sanagi—workers exposed for an average of 6.2 years to solvent vapors consisting of an eight hour time weighted average of 58 ppm (+/- 41 ppm) n-hexane and 39 ppm (+/- 41 ppm) acetone.
- Critical Effects:
  1. experimental—Miyagaki—electromyography, strength duration curves, electrical reaction time, and flexor/extensor chronaxy ratio, gait posture and muscular atrophy were studied. Increased complexity of neuromuscular unit voltages during electromyographic analysis was noted in 0/6 controls, 1/6 in the

100 ppm group, 3/6 in the 250 ppm group, 5/6 in the 500 ppm group, 3/3 in the 1000 ppm group, and 4/4 in the 2000 ppm group. A dose related increase in incidence and severity of reduced interference voltages from muscles was noted in mice exposed to 250 ppm or more, but not in controls (0/6 examined) or in the 100 ppm group (0/6). Dose related abnormal posture and muscle atrophy were noted at 250 ppm or more. This study identifies a NOAEL of 100 ppm for neurotoxicity (68 ppm when adjusted for 67.5% n-hexane).

2. occupational:
    - Chang—symptomatic peripheral neuropathy was noted in 20 of 56 workers, while another 26 has evidence of subclinical neuropathy. Reduced sensory action potentials; reduced motor action potentials, decreased motor nerve conduction velocity, and increased distal latency were found in most workers.
    - Sanagi—no overt neurological abnormalities were noted, the mean motor nerve conduction velocity and residual latency of the exposed group were significantly decreased as compared to unexposed workers. The study reports a LOAEL of 58 ppm n-hexane.

- LOAEL—250 ppm (from Miyagaki)
- NOAEL—100 ppm (68 ppm when adjusted for 67.5% n-hexane)
- Human equivalent concentration—58 ppm (204,740 ug/m^3)
  (100 ppm x 0.675 x 6/7)
- Uncertainty factors:
    1. LOAEL uncertainty factor 1
    2. subchronic uncertainty factor 1
    3. interspecies uncertainty factor 3
    4. intraspecies uncertainty factor 10
    5. cumulative uncertainty factor 30

US EPA (2005)

RFC **700 ug/m^3**

Derivation Information:

- Study—Huang, J., Kato, K., Shibata, E., et al. 1989. Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. Arch. Toxicol. 63: 381-385.
- Study format—male Wistar rats (eight per group) were exposed to 0, 500, 1200, or 3000 ppm [0, 1762, 4230, 10574 mg/m3] n-hexane (>99 per cent pure) for 12 hours/day, 7 days/ week for sixteen weeks.

- Critical effects—study measured motor nerve conduction velocity in the tail nerve along with body weight before exposure and after 4, 8,12 and 16 weeks to n-hexane, and measured the levels of neuron specific enolase and beta-S-100. A dose dependant statistically significant reduction in body weight gain was observed in the mid-dose (at 12 weeks) and high-dose (at 8 weeks) rats. There were some neurological deficits in the mid-dose and high-dose, including a reduction in grip strength and a comparative slowness of motion from week 12 of exposure. Among the biochemical changes there were dose dependant reductions in nervous system proteins, particularly the beta-S-100 proteins in tail nerve fibers, which were reduced approximately 75 per cent at all dose levels.
- BMCL—430 mg/m^3
- $BMCL_{ADJ}$—215 mg/m^3
- $BMCL_{HEC}$—215 mg/m^3
- Uncertainty factors:
    1. intraspecies uncertainty 10
    2. interspecies uncertainty 3
    3. less than lifetime uncertainty 3
    4. database uncertainty 3
    5. cumulative uncertainty 300

ATSDR (1999)

MRL 2118 ug/m^3

Derivation Information:

Study-Sanagi, S., Seki, Y., Sugimoto, K. et al. 1980. Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int. Arch. Occup. Environ. Health. 47:69:79.

See above for format and critical effects.

- Uncertainty factors:
    1. LOAEL uncertainty 10
    2. intraspecies uncertainty 10
    3. cumulative uncertainty 100

Discussion:

The California document "Chronic Toxicity Summary—N-HEXANE" contains the following:

"The major strengths of the REL for hexane include: (1) the primary use of an animal study (Miyagaki) with controlled, nearly continuous chronic hexane exposures not

confounded by coexposure to other solvents, which observed both a NOAEL and LOAEL; and (2) the results obtained from two different human studies (Sanagi and Chang) which were viewed as being generally consistent with the animal study based REL."

The EPA document "Toxicological Review of n-HEXANE" contains the following:

"…Huang et al. evaluated a comprehensive array of neurological endpoints and an adequate number of animals and exposure groups and was of the appropriate quality for the derivation of the RFC."

Note that CalEPA looked at the Huang study and presumably did not use it because it did not have a NOAEL and the Miyagaki study had a lower LOAEL than the Huang study. (However, U. S. EPA cites 500 ppm as a NOAEL in the Huang study.) U. S. EPA did not discuss the Miyagaki study.

VINTAG expressed was some concern about the human studies (California supporting studies) and co-exposure with acetone in addition to hexane. However, California did not use the human studies quantitatively in the development of the REL.

ATSDR did use a human study (Sangai, et. al.) to derive the MRL. ATSDR also discusses the concern that acetone exposure may potentiate n-hexane toxicity. However, this would underestimate the MRL. (The level of n-hexane alone required to produce the same effects would be higher.)

There was also concern with the EPA study and the relevance of the S-100 protein measurements to humans. However, on closer reading of the EPA evaluation, it appears that the decrease in the protein was not actually used as a critical effect in deriving the RfC.